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Preoperative prediction of the extrathyroidal extension of papillary thyroid carcinoma with ultrasonography versus MRI: A retrospective cohort study

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ABSTRACT

Background: The purpose of this study was to assess the diagnostic performance of preoperative ultrasonography (US) for the prediction of extrathyroidal extension (ETE) in patients with papillary thyroid carcinoma (PTC) and to compare the diagnostic performances of US and magnetic resonance imaging (MRI) for predicting ETE.

Methods: 75 patients with PTC who underwent preoperative US and MRI were retrospectively reviewed in this study. Two radiologists independently evaluated the US and MR findings to assess minimal or extensive ETE of PTC. These results were compared with the histopathologic findings. The diagnostic performances of US and MRI in the evaluation of ETE were compared.

Results: US was more accurate than MRI in the prediction of minimal ETE ($p < 0.05$) and the accuracies were not significantly different between US and MRI in extensive ETE. US showed higher sensitivity, negative predictive value and accuracy than MRI ($p < 0.001$) in the prediction of overall ETE.

Conclusion: US provided higher accuracy for assessing overall ETE and higher sensitivity for minimal ETE than MR imaging in preoperative evaluation of ETE of PTC. There was no significant difference in evaluating extensive ETE of PTC between US and MRI.

1. Introduction

High-resolution ultrasonography (US) can characterize thyroid nodules and visualize the adjacent tissue and organs around thyroid gland clearly. US has been a modality of choice for preoperative evaluation of papillary thyroid carcinoma (PTC). The extent of surgery was determined based on the preoperative staging of PTC and preoperative staging US is essential for surgical planning and predicting patient outcome [1–3]. Preoperative staging of PTC was assessed, based on TNM classification of the American Joint Committee on Cancer and the International Union Against Cancer, 7th [4].

Extra-thyroidal extension (ETE) of PTC is an independent risk factor associated with increased risk of morbidity and mortality [5]. According to TNM classification, minimal ETE (T3) was defined as extension into sternothyroid muscle or perithyroid soft tissue by the tumor and extensive ETE (T4) was defined as gross extension to subcutaneous soft tissues, larynx, trachea, esophagus, recurrent laryngeal nerve, or major vessels by the tumor. Previous studies reported that massively invasive carcinomas and older age carry a significantly higher mortality than tumors with minimal invasion [6]. Therefore, the presence of ETE is a critical prognostic factor with implications for the aggressiveness of primary surgical excision and preoperative assessment of ETE is important in planning surgical extent.

Several studies have been conducted to assess the usefulness of various imaging techniques including US, CT or MRI for the evaluation of ETE of thyroid cancer to the adjacent structures [7–13]. Previous studies have reported about the diagnostic performance of preoperative US for determination of ETE of PTC [14–16]. Although US has high sensitivity predicting ETE, US is an operator dependent procedure and US has some limitations in evaluating large sized tumor, densely calcified tumor or massive ETE. MRI has been considered as a complementary method for the evaluation of large tumor or extensive ETE. Therefore, we tried to evaluate the diagnostic performance of US and MRI for assessing the ETE of PTC.

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The purposes of this study were to assess the diagnostic performance of preoperative US for prediction of ETE in patients with PTC and to compare the diagnostic performances of US and MRI for predicting ETE.

2. Materials and methods

This retrospective study was conducted with institutional review board approval and a waiver of patient informed consent.

2.1. Patients

We reviewed our data base from January 2011 to May 2012 and identified 79 patients with surgically confirmed PTC who underwent both preoperative staging US and MRI for the evaluation of PTC at our institute. 4 patients were excluded on the basis of following criteria; 3 patients who had underwent previous hemi- or total thyroidectomy and one patient with a follicular carcinoma. Thus, our study included 75 patients (23 men, 52 women; age range, 19–88 years; mean, 45.5 ± 12.1 years) with PTC.

2.2. US examination

US was performed with 5- to 12 MHz linear array transducer (iU22; Philips Medical Systems) or 4–15-MHz linear array transducer (SuperSonic Imagine, Aix-en-Provence, France). At our institute, all patients with thyroid malignancy underwent preoperative staging US before surgery. Preoperative staging US examinations were performed by one of six board-certified radiologists with 3–15 years of experience in thyroid imaging and the staging was prospectively reported according to TNM staging [4].

2.3. MRI examination

Preoperative MRI was performed if ETE was suspected by clinical findings of huge mass, hoarseness or physical examination. MRI was performed with a 1.5-T Avanto (Siemens, Erlangen, Germany) MR unit using a neck coil. T1-weighted images (758/7.9; excitations, 1) and conventional spin-echo T2-weighted images (3500/115; excitations, 1) were obtained in the axial plane. From the level of the mandibular angle to the sternal notch were obtained with a slice thickness of 3 mm and an intersection gap of 1–2 mm. Axial T1-weighted spin-echo sequences were repeated, using a 256 or 512 matrix, after an intravenous bolus injection of 0.2 mmol/kg gadoterate meglumine (Gd-DOTA, DOTAREM, Guerbet, Roissy CdG Cedex, France). In addition, a sagittal T1-weighted spin-echo and an axial T1 sequence with fat suppression (SPIR) were performed in all patients, following intravenous contrast.

2.4. Image analysis of ETE

All US and MR images were retrospectively reviewed by two radiologists (H. Kim and J. Kim) independently with regard to the minimal ETE and invasion into the surrounding tissue of trachea, esophagus, common carotid artery (CCA), internal jugular vein (IJV), and recurrence laryngeal nerve (RLN). Both readers were blinded to the surgical and pathologic findings but they were informed about the location and size of the index malignancy in patients with multiple thyroid lesions. The review of US and MR images was performed independently with 2 weeks interval.

With US, minimal ETE of PTC was suggested when one of the following US criteria was full-filled: focal bulging out or disruption of the thyroid capsule by tumor was observed or more than 25% of perimeter of the tumor was abutting the thyroid capsule (Fig. 1) [15–17]. Invasion of trachea was suggested when obliteration of echogenic layer between the tracheal adventitia and thyroid

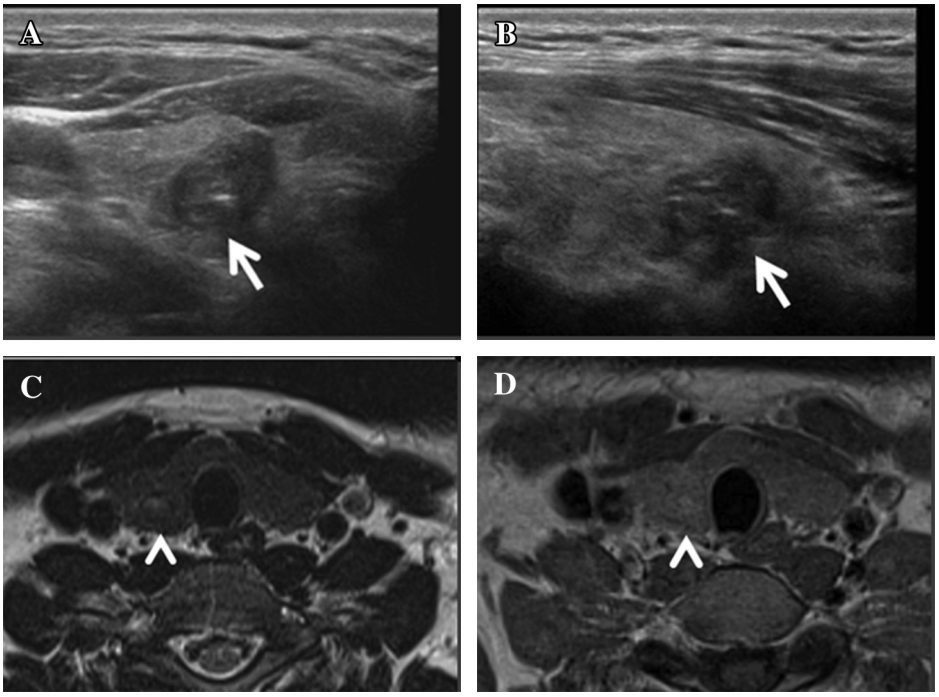

Fig. 1. 42 year-old man with a papillary thyroid carcinoma (PTC) with minimal extrathyroidal extension (ETE). US images of transverse view (A) and longitudinal view (B) show a hypoechoic nodule abutting the posterior thyroidal capsule (arrow) more than 25% of its perimeter and which suggests the minimal ETE of PTC. T2-weighted (C) and enhanced T1-weighted (D) MR images show a nodule as an intrathyroidal lesion (arrow head). Surgery revealed a PTC with minimal ETE.

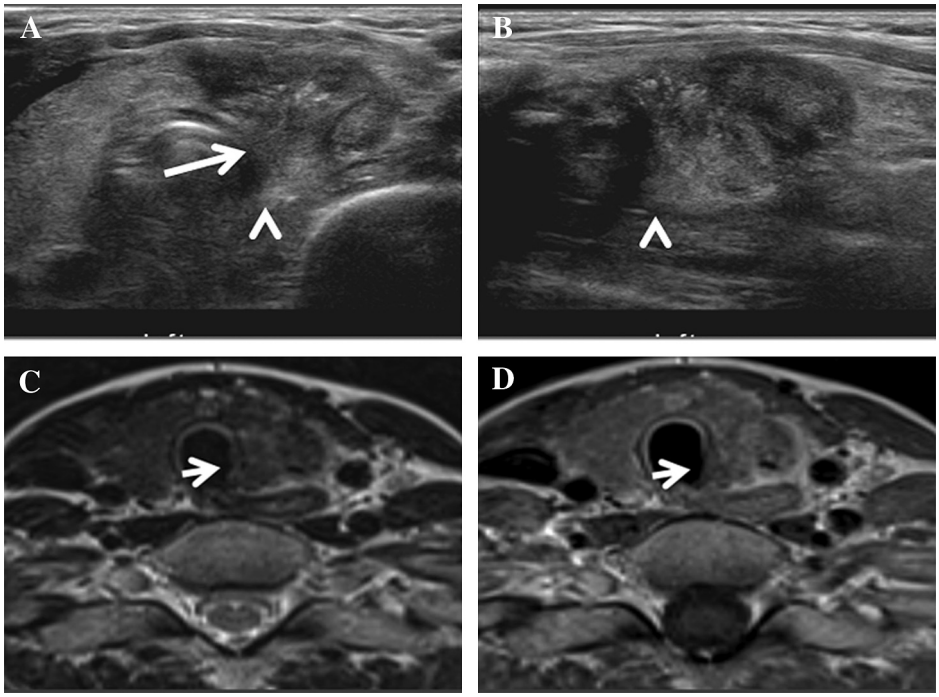

Fig. 2. 48 year-old woman with papillary thyroid carcinoma (PTC) with extensive extrathyroidal extension (ETE). US images of transverse view (A) and longitudinal view (B) show a mass obliterating the hypoechoic cartilaginous layer of tracheal wall (arrow) and a tumor occupying the tracheal esophageal groove (arrow head), which suggest the invasion of recurrent laryngeal nerve. T2-weighted (C) and enhanced T1-weighted (D) MR images show soft tissue signal intensity (short arrow) at the lateral aspect of tracheal wall suggesting tracheal wall invasion. Surgery revealed a PTC invading tracheal wall and left recurrent laryngeal nerve.

capsule or dilatation of hypoechoic layer of cartilaginous space by tumor was observed (Fig. 2) [8]. Invasion of esophagus was suggested if loss of normal esophageal layer by tumor was observed [18]. Invasion of the major vessels was suggested if the tumor was in contact with 180° or more of the circumference of the vessel and tumor invasion into the vessels lumen [17,18]. Invasion of RLN was suggested when a tumor occupying the tracheal esophageal groove was observed (Fig. 2) [18].

With MRI, minimal ETE of thyroid cancer was suggested when tumor showed poorly defined margin with heterogeneous signal intensity in adjacent soft tissue, focal bulging out or disruption of the thyroid capsule by tumor was observed or more than 25% of perimeter of the tumor was abutting the thyroid capsule [16,17]. Invasion of the trachea was suggested when soft tissue signal intensity obliterating the tracheal wall on T2-weighted images or contrast enhanced T1-weighted images or intraluminal mass by tumor invasion was observed (Fig. 2) [8,11]. Invasion of esophagus was suggested if tumor invasion into the esophageal lumen or loss of normal esophageal layer by tumor was observed [18]. Invasion of the major vessels was suggested if tumor was in contact with 180° or more of the circumference of the vessel [11,17]. Invasion of RLN was suggested when completely effaced fatty tissue in tracheal esophageal groove by tumor was observed [13].

2.5. Statistical analysis

Minimal ETE or extensive ETE at US and MRI were analyzed with histopathologic findings as the standard of reference. Diagnostic performances of sensitivity, specificity, PPV, NPV, and accuracy of US and MRI were calculated for minimal ETE, extensive ETE and overall ETE (minimal and extensive ETE). Diagnostic performances of US and MRI were also calculated for the invasion adjacent organs including trachea, esophagus, major vessels invasion including CCA or IJV, and RLN. Logistic regression with GEE (Generalized estimating equation) method or WLS (Weighted Least Square) method were used to compare the diagnostic performances of US and MRI for the ETE of thyroid cancer. For all tests, $p < 0.05$ was considered to indicate a statistically significant difference.

Interobserver agreement was determined by calculating kappa values for assessing ETE of PTC. A kappa value of 0, indicated poor agreement; 0.01–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, good agreement; and 0.81–1.00, excellent agreement [19]. Statistical analysis was performed with software (version 9.1.3, SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Surgicopathological diagnosis of ETE

All patients underwent complete resection of the primary tumor; 8 patients had intrathyroidal PTCs (4 in T1 tumors, 4 in T2 tumors) and 67 patients had PTCs with ETE. Among 67 thyroid cancers with ETE, 53 had minimal ETE and 14 had extensive ETE according to the surgical and histopathologic findings. Direct invasion of adjacent organs was found in 14 patients; invasion of trachea ($n = 10$), esophagus ($n = 7$), CCA or IJV ($n = 7$) and RLN ($n = 1$).

The pathologic types of PTCs were conventional ($n = 69$), diffuse sclerosing variant ($n = 3$), follicular variant ($n = 2$), and tall cell variant ($n = 1$).

3.2. Diagnostic performance of US and MRI for the assessment of ETE

Table 1 shows the diagnostic performance of US and MRI in the evaluation of ETE of PTC. For the evaluation of minimal ETE, US showed higher sensitivity ($p = 0.006$) and less specificity than MRI

Table 1
Diagnostic performance of US and MRI for the assessment of extrathyroidal extension of papillary thyroid carcinoma.

Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy
Minimal (T3)					
US	80.1	70.4	86.3	59.6	77.3
MRI	64.7	84.9	90.6	50.0	70.4
p	0.006	0.039	0.220	0.094	0.113
Extensive (T4)					
US	78.5	79.5	46.8	94.1	79.3
MRI	89.2	76.8	47.1	96.8	79.1
p	0.176	0.517	0.219	0.219	0.857
Overall					
US	100.0	71.2	92.4	100.0	92.6
MRI	88.7	77.5	92.1	68.5	83.2
p	<0.001	0.306	0.738	<0.001	<0.001

PPV: positive predictive value.
NPV: negative predictive value.

($p = 0.039$). For extensive ETE, there were no significant differences in sensitivity, specificity, PPV, NPV and accuracy between US and MRI (Table 1). For overall ETE, US showed higher sensitivity, NPV and accuracy than MRI ($p < 0.001$) (Table 1). The specificity and PPV were not significantly different between US and MRI. Table 2 summarizes the diagnostic performance of US and MRI for the prediction of direct tumor invasion into adjacent structures.

Interobserver agreement was moderate for overall ETE of thyroid cancer with kappa values of 0.79 (range, 0.75–0.83) on US and 0.65 on MRI (range, 0.61–0.70).

4. Discussion

The majority of patients with thyroid carcinoma have tumors with well differentiated histology and they have an excellent overall prognosis. However, 11.5%–30% of these tumors can display ETE, which is associated with an increased incidence of local recurrence, regional and distant metastasis, and decreased survival [20–22]. Hay et al. audited 2444 Mayo clinic PTC patients and found that 328 (13%) patients had ETE at first presentation [23]. An earlier audit of 262 Mayo Clinic patients with ETE found that two or more extra-thyroidal sites were frequently involved [24]. They found invasion of sternothyroid muscle in 53%, RLN in 47%, trachea 37% and esophagus 21%. Ito et al. graded overall ETE according to the pathology and intraoperative surgical findings and they classified ETE into minimal ETE and extensive ETE [22]. Extensive ETE emerged as an independent prognostic factor for relapse-free survival, however, patients with minimal ETE had similar relapse free survival with patients without ETE. The American Joint Committee on Cancer staging system has become quite explicit about the extent of ETE, differentiating it into T3 and T4 based on the degree of ETE, and which is especially an issue for patients over 45 years of age [4]. Therefore, precise assessment of ETE is crucial in preoperative staging of thyroid cancer with US, CT or MRI.

Table 2
Diagnostic performance of US and MRI for the prediction of direct invasion into adjacent structures by papillary thyroid carcinoma.

Structure Invaded	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy
Trachea					
US	63.6	85.1	42.4	93.1	82.0
MRI	59.0	82.6	37.1	92.1	79.1
Esophagus					
US	35.7	96.3	50.0	93.5	90.6
MRI	57.1	92.5	44.4	95.4	89.2
Major vessels					
US	35.7	97.7	62.5	93.6	92.0
MRI	42.8	96.2	54.5	94.2	91.2
RLN					
US	50.0	97.2	20.0	99.3	96.6
MRI	50.0	95.9	14.2	99.2	95.3

PPV: positive predictive value.
NPV: negative predictive value.
RLN: recurrent laryngeal nerve.

There have been several previous studies about comparison of US and CT in preoperative staging of PTC [14]. To the best of our knowledge, there have been few studies evaluating the diagnostic performance of MRI in assessing ETE by thyroid cancer, compared with that of US. In this study, we evaluated the diagnostic performance of preoperative US and MRI for predicting ETE of PTC and compared the diagnostic performances between the two modalities. We observed that US showed higher sensitivity (80% vs. 64.7%) and lower specificity (70.4% vs. 84.9%) than MRI for predicting minimal ETE of PTC. Five PTCs were not visualized with MRI (Tx) by two observers and three of them were confirmed as T1 tumors and two were confirmed as T3 tumors. US can provide greater spatial resolution than CT or MRI and better visualization of normal thyroid capsule. With this reasons, we suggest that US has higher sensitivity for assessing minimal ETE than MRI.

In this study, the diagnostic performance of US was comparable with MRI in the assessment of extensive ETE ($p > 0.05$) and we observed US had significantly higher sensitivity (100%), NPV (100%) and accuracy (92.6%) than MRI in the prediction of overall ETE ($p < 0.001$). Several studies have reported the usefulness of US and MRI for the preoperative evaluation of tracheal invasion [10,11,25]. Yamamura et al. reported that accuracy of US for the diagnosis of tracheal invasion by PTC was 83.3% [7]. Tomoda et al. reported significantly higher sensitivity, specificity, NPV with US (91%, 93%, 25%, 99% and 93%) than with MRI (83%, 70%, 71%, 91% and 73%) in the preoperative evaluation of extensive ETE, especially in the prediction of tracheal invasion of PTC [8]. Our data showed the accuracy of US for the diagnosis of tracheal invasion was 82.0% which was similar to the previous studies. In this study, the diagnostic performance of US was superior to MRI in evaluation of tracheal invasion of PTC. It is more difficult to identify the early stage of tracheal invasion by MRI than by US because tracheal adventitia is thin and the motion artifact of MRI degrades the image, especially when the PTC is small. We assumed that subtle disruption of aerodigestive wall such as esophagus is easier to be visualized with US rather than with MRI. However, our study showed that lower sensitivity (35.7%) of US for evaluation of esophageal invasion, compared with that of MRI (57.1%). With higher contrast resolution of MRI, two or three layer structure of normal esophagus is well defined with preserved fat planes, whereas, US is limited in evaluating esophagus which is mostly located at the mid-line or at the left posterior aspect of trachea. Our data showed relatively inferior sensitivity of MRI (57.1%) for the prediction of esophageal invasion of PTC, compared with the previous result which reported 82% of sensitivity [12]. The mean tumor size of 75 thyroid carcinomas was 1.9 ± 0.7 cm (range: 0.5–7.2 cm) in our study and the relatively smaller size of thyroid cancers could have affected the diagnostic performance of MRI in this study. Further prospective study with a larger case scale is necessary to validate our result.

Our study has several limitations. First, this study is a retrospective study and a selection bias may exist because included patients underwent MRI when ETE was suggested clinically even though which was usual in clinical situation. Second, this study included a small number of cases who have tumors invading into the trachea, esophagus, major vessels and RLN. This low prevalence may have limited the calculated descriptive statistics for each of the structures affected by ETE. Therefore, we recommend randomized prospective studies with both US and MRI evaluation of PTC to

validate our study results and compare the diagnostic performance of US and MRI for predicting ETE.

In conclusion, US provided higher accuracy for assessing overall ETE and higher sensitivity for minimal ETE than MRI in the preoperative assessment of ETE of PTC. There was no significant difference of diagnostic performance in evaluating extensive ETE between US and MRI.

Ethical approval

This retrospective study was conducted with institutional review board approval and a waiver of patient informed consent.

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Author contribution

Study concepts: Jeong-Ah Kim, Hana Kim.

Study design: Jeong-Ah Kim, Hana Kim.

Data acquisition: Jeong-Ah Kim, Hana Kim, Eun Ju Son, Ji Hyun Youk, Hang-Seok Chang.

Quality control of data and algorithms: Jeong-Ah Kim, Hana Kim.

Data analysis and interpretation: Jeong-Ah Kim, Hana Kim, Cheong Soo Park.

Statistical analysis: Jeong-Ah Kim, Hana Kim.

Manuscript preparation: Jeong-Ah Kim, Hana Kim, Hang-Seok Chang.

Manuscript editing: Hana Kim, Jeong-Ah Kim, Eun Ju Son, Cheong Soo Park.

Manuscript review: Jeong-Ah Kim, Eun Ju Son, Ji Hyun youk, Hana Kim, Tae-Sub Chung.

Conflict of interest

The authors declare that they have no competing interests.

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